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=> d his

     (FILE 'HOME' ENTERED AT 11:24:02 ON 17 JUL 2003)

     FILE 'EUROPATFULL, PATDPAFULL, PCTFULL, RDISCLOSURE, USPATFULL, USPAT2'
     ENTERED AT 11:24:17 ON 17 JUL 2003
                E BOEHRINGER/PA
L1          7391 S E3-E12
L2          1006 S  L1 AND (?NEOPLASTIC OR ANTI(W)TUMOR? OR ANTITUMOR? OR CANCER
L3            34 S L2 AND ANTHRACYCLINE
L4             0 S L3 AND (AROMATASE OR EXEMESTANE OR FORMESTANE OR ANASTROZOLE
L5             0 S L2 AND (AROMATASE OR EXEMESTANE OR FORMESTANE OR ANASTROZOLE
L6          2424 S (AROMATASE OR EXEMESTANE OR FORMESTANE OR ANASTROZOLE OR LETR
L7           746 S (?NEOPLASTIC OR ANTI(W)TUMOR? OR ANTITUMOR? OR CANCER# OR CHE

     FILE 'USPATFULL' ENTERED AT 11:35:26 ON 17 JUL 2003
L8           273 S L7
L9             4 S L8 NOT PY>=1999

     FILE 'EUROPATFULL, PATDPAFULL, PCTFULL, RDISCLOSURE, USPATFULL, USPAT2'
     ENTERED AT 11:47:37 ON 17 JUL 2003
                E PHARMACIA/PA
L10         3453 S E3-E12
L11           55 S L10 AND L7
L12           31 S L11 AND ANTHRACYCLINE
L13            0 S L12 NOT PY>=1999

     FILE 'USPATFULL, USPAT2' ENTERED AT 11:55:09 ON 17 JUL 2003
L14            8 S L12
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8,944,460

SUMM Most preferred is one or more of the **chemotherapeutics** selected from the group comprising cisplatin, mitomycine and vinblastine.

SUMM . . . that "responds to modulation of PKC activity" there is preferably meant a proliferative disease selected from hyperproliferative conditions such as **cancers**, tumors, hyperplasias, fibrosis (espeically pulmonary fibrosis, but also other kinds of fibrosis, such as renal fibrosis), angiogenesis, psoriasis, atherosclerosis and. . .

SUMM Most preferably, the disease is one selected from **cancer** types which have been very difficult to treat or even practically unaffected by therapy with standard **chemotherapeutics**, such as small cell lung carcinoma, large cell lung carcinoma, melanoma, prostate carcinoma or further also lymphoma. Most preferably, any. . . inhibition of human PKC-.alpha. activity is meant. Treatment of prostate carcinomas, lung carcinomas, especially large lung cell carcinomas, or breast **cancer** is especially preferred.

SUMM b) at least one other **chemotherapeutic** agent where any component a) and/or b).can also be present in the form of a pharmaceutically acceptable salt, if at. . .

SUMM . . . cells and the remaining blood cells of the immune system may be destroyed in the subject e.g. by irradiation or **chemotherapy** and then the selected normal cells may be reimplanted into the subject, e.g. by injection etc. The methods to be. . .

SUMM Provided that salt-forming groups are present, the ODN as well as the other **chemotherapeutic**(s) may also be present in the form of salts.

SUMM . . . salt-forming group is present, it is also possible that mixed salts are present. Corresponding salts can be formed from other **chemotherapeutic** agents provided that salt-forming groups are present therein.

SUMM The **antitumor** activity of SEQ-ID NO: 1-ODN as single agents is tested against various human tumors transplanted subcutaneously into nude mice. The. . . 30 at doses of 6, 0.6, 0.06, 0.006 mg/kg. In all tumor types tested, the SEQ-ID NO: 1-ODN exhibits significant **antitumor** activity in the dose range of 0.06-6.0 mg/kg. The most sensitive tumor is A549 lung carcinoma (significant activity at 0.006. . . bladder and MDA-MB-231 breast carcinoma and Colo 205 colon carcinoma. transplanted into nude mice (significant activity at 6 mg/kg). The **antitumor** effects of the SEQ-ID NO: 1-ODN are sequence-specific since scrambled control ODNs do not show **antitumor** effects. A scrambled phosphothioate control (same base composition, but in totally different sequence) ODN to SEQ-ID NO: 1-ODN did not show **antitumor** activity in T24 bladder and A549 lung carcinomas, indicating that the **antitumor** effects of the SEQ-ID NO: 1-ODN in vivo are specific and sequence-dependent.

SUMM The eff

plicamycin (Mithracin, formerly called Mithramycin) and preferably cross-linking (bis-alkylating) **antitumor** antibiotics, such as mitomycin C (Mitomycin, Mutamycin);

SUMM . . . leuprolide (Lupron, Lupron Depot); anti-androgens such as flutamide (Eulexin); anti-estrogens such as tamoxifen; aromatase inhibitors such as aminogluthetimide (Cytadren), lentaron (**Formestane**, 4-hydroxy-4-androsten-3,17-dione) (see EP 0 162 510), **fadrozole** (5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo [1,5-a]pyridin, see EP 0 437 415 and EP 0 165 904), **letrozole** (4,4'-(1H-1,2,4-triazol-1-yl-methylen)-bis-benzonitrile, see U.S. Pat. No. 4,976,672), 4-(.alpha.-(4-cyanophenyl)-.alpha.-fluoro-1-(1,2,4-triazolyl)methyl)-benzonitrile (see EP 0 490 816) or 4-(.alpha.-(4-cyanophenyl)-(2-tetrazolyl)methyl)-benzonitrile (see EP 0 408 509); adrenal. . .

SUMM . . . retinoic acid (TRA); immunomodulators, such as levamisole (ergamisol); vaccines, e.g. anti-melanoma vaccines (see EP 0 674 097); or antibodies with **antitumor** activity, such as recombinant human immunoglobulins directed at melanoma antigen (see EP 0 640 131) or antibodies for active imm

SUMM . . . the molecular basis of mammalian cell transformation has led to the unifying concept of growth regulation and its disorders in **cancer** cells. The fact that many products of "**cancer** genes" encode for proteins that regulate normal mitogenesis suggests that the carcinogenic process may be viewed as a multistep and. . . strategy is, consequently, based on the assumption that blocking deregulated mitogenic signal transduction at the level of PKs will cause **cancer** growth inhibition. This approach is likely to identify compounds with less side effects compared to standard **chemotherapeutic** agents.

SUMM Protein kinase C (PKC) has attracted attention as a target for **cancer** drug development for a number of reasons. PKC is a primary receptor for the tumor-promoting phorbol esters and PKC levels. . . In addition, these drugs interfering with intracellular signaling are expected to have far less unwanted side effects than the classical **chemotherapeutic** agents that are currently used. The phosphotioate antisense oligonucleotide that corresponds to the sequence 5'-GTT CTC GCT GGT GAG TTT. . . which inhibits the expression of PKC-.alpha. mRNA and protein both in vitro and in vivo. SEQ-ID NO: 1-ODN shows potent **antitumor** activity in nude mice in vivo as a single agent. In addition, additive and even synergistic effects between PKC-.alpha. ODNs and standard **chemotherapeutic** drugs have been observed in nude mouse xenograft models. SEQ-ID NO: 1-ODN might therefore be used both as a single agent and in combination therapy for the treatment of **cancer**.

SUMM Surprisingly, positive and preferably even highly synergistic effects between PKC-, especially PKC-.alpha.-targeted oligonucleotides or oligonucleotide derivatives (ODNs) and standard **chemotherapeutic** drugs have been observed in nude mouse xenograft models. It is thus reasonable to assume that the ODNs might be used not only as single agents, but also especially in combination therapy for the treatment of **cancer** diseases.

SUMM This combination offers a lot of advantages: In the first place, standard **chemotherapeutics** often display significant side effects up to really toxic effects, so that their use alone is often very difficult in. . . use and side effects. In the new combinations decribed herein, however, it is possible to diminish the amount of standard **chemotherapeutic** needed and thus to alleviate side effects. Second, the ODNs have a very high tolerability (up to 100 mg/kg have been found to be non-toxic in animals), thus allowing great flexibility in the treatment of **cancer** patients. Third, due to the fact that the PKC-, especially PKC-.alpha.-directed ODNs open up a totally new route of treatment, it is also possible to treat **cancer** types which have been very difficult to treat or even practically unaffected by therapy with standard **chemotherapeutics**, such as small cell lung carcinomas, large cell lung carcinomas, melanomas, prostate carcinomas and also breast **cancer**. Fourth, in a number of cases it is even possible to bring about regression of tumors and complete cure. Most. . .

SUMM . . . one oligonucleotide or oligonucleotide derivative (ODN) targeted to nucleic acids encoding (especially human) PKC with b) at least one other **chemotherapeutic** agent; or pharmaceutically acceptable salts of any component a), b) or a) and b) if at least one salt-forming group. . .

SUMM . . . nucleic acids encoding (especially human) PKC and capable of modulating (especially human) PKC expression and b) at least one other **chemotherapeutic** agent are administered to a mammal in combination in a quantity which is jointly therapeutically effective against proliferative diseases that. . .

SUMM b) at least one other **chemotherapeutic** agent where any component a) and/or b).can also be present in the form of a pharmaceutically acceptable salt, if at. . .

SUMM b) at least one other **chemotherapeutic** agent, where any

component a) and/or b) can also be present in the form of a pharmaceutically acceptable salt, if. . .

SUMM b) at least one other **chemotherapeutic** agent, where any component a) and/or b) can also be present in the form of a pharmaceutically acceptable salt, if. . .

SUMM The term "at least one" taking reference to a) oligonucleotides or oligonucleotide derivatives or b) other **chemotherapeutic** agents refers to one or more, especially 1 to 5, members of each group a) or b), preferably to one. . .

SUMM By the term "other **chemotherapeutic** agent" there is meant any **chemotherapeutic** agent except for antisense oligonucleotides or oligonucleotide derivatives targeted to raf-kinase that is or can be used in the treatment of tumor diseases, such as **chemotherapeutics** derived from the following classes:

SUMM . . . nitrosoureas such as cyclohexylnitrosourea (meCCNU; Carmustine, BCNU, BiCNU) or lomustine (CCNU, CeeNU), cis-platinum(II)-diaminedichloride (platinol or cisplatin); carboplatin (Paraplatin); preferably cross-linking **chemotherapeutics**, preferably bis-alkylating agents, especially nitrogen mustards, such as mechlorethamine (Mustargen); alkyl sulfonates such as busulfan (Myeleran); cyclophosphamide; melphalan (Alkeran); chlorambucil. . .

SUMM (B) **antitumor** antibiotics, preferably selected from the group comprising bleomycine (Blenoxane); anthracyclines, such as daunomycin, dactinomycin (Cosmegen), daunorubicin (Cerubidine), doxorubicin (Adriamycin, Rubex), epirubicin, esorubicin, idarubicin (Idamycin), plicamycin (Mithracin, formerly called Mithramycin) and preferably cross-linking (bis-alkylating) **antitumor** antibiotics, such as mitomycin C (Mitomycin, Mutamycin);

SUMM . . . leuprolide (Lupron, Lupron Depot); anti-androgens such as flutamide (Eulexin); anti-estrogens such as tamoxifen; aromatase inhibitors such as aminogluthetimide (Cytadren), lentaron (**Formestane**, 4-hydroxy-4-androsten-3,17-dione) (see EP 0 162 510), **fadrozole** (5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo [1,5-a]pyridin, see EP 0 437 415 and EP 0 165 904), **letrozole** (4,4'-(1H-1,2,4-triazol-1-yl-methylen)-bis-benzonitrile, see U.S. Pat. No. 4,976,672), 4-(.alpha.-(4-cyanophenyl)-.alpha.-fluoro-1-(1,2,4-triazolyl)methyl)-benzonitrile (see EP 0 490 816) or 4-(.alpha.-(4-cyanophenyl)-(2-tetrazolyl)methyl)-benzonitrile (see EP 0 408 509); adrenal. . .

SUMM . . . retinoic acid (TRA); immunomodulators, such as levamisole (ergamisol); vaccines, e.g. anti-melanoma vaccines (see EP 0 674 097); or antibodies with **antitumor** activity, such as recombinant human immunoglobulins directed at melanoma antigen (see EP 0 640 131) or antibodies for active immunotherapy. . .

SUMM More preferred is any of the above-mentioned **chemotherapeutic** agents except for oligonucleotide derivative targeted at PKC, adriamycin (doxorubicin) and cyclophosphamide, preferably alone, or more preferably alone or in. . .

SUMM Especially preferred are the **chemotherapeutic** agents mentioned above under (A) as cross-linking **chemotherapeutics**, preferably bis-alkylating agents, especially nitrogen mustards, such as mechlorethamine (Mustargen); alkyl sulfonates such as busulfan (Myeleran); cyclophosphamide; melphalan (Alkeran); chlorambucil. . . carboplatin (Paraplatin); or compounds that form cross-links via ionic bonds, such as ethyleneimine derivatives, e.g. triethylenethiophosphoramid (thio-tepa) (forms ionic cross-links); **chemotherapeutic** agents mentioned under (B) as cross-linking (bis-alkylating) **antitumor** antibiotics, such as mitomycin C (Mitomycin, Mutamycin); or vinca alkaloids, such as vinblastine (Velban), vincristine (Oncovin) or vindesine.

SUMM Preferably, the term "other **chemotherapeutic** agent" relates to a standard **chemotherapeutic** agent as mentioned before that is already used clinically, or in a less preferred sense also to a **chemotherapeutic** agent that is already being tested clinically.

mitomycin C (Mitomycin, Mutamycin);

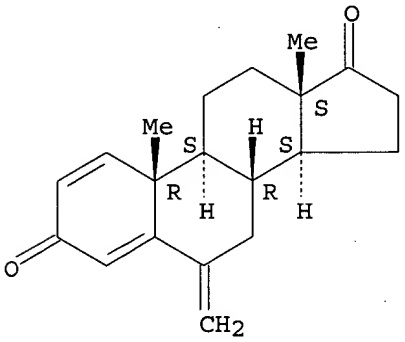
SUMM . . . leuprolide (Lupron, Lupron Depot); anti-androgens such as flutamide (Eulexin); anti-estrogens such as tamoxifen; aromatase inhibitors such as aminogluthetimide (Cytadren), lentaron (**Formestane**, 4-hydroxy-4-androsten-3,17-dione) (see EP 0 162 510), **fadrozole** (5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo [1,5-a]pyridin, see EP 0 437 415 and EP 0 165 904), **letrozole** (4,4'-(1H-1,2,4-triazol-1-yl-methylen)-bis-benzonitrile, see U.S. Pat. No. 4,976,672), 4-(.alpha.-(4-cyanophenyl)-.alpha.-fluoro-1-(1,2,4-triazolyl)methyl)-benzonitrile (see EP 0 490 816) or 4-(.alpha.-(4-cyanophenyl)-(2-tetrazolyl)methyl)-benzonitrile (see EP 0 408 509); adrenal. . .

SUMM . . . retinoic acid (TRA); immunomodulators, such as levamisole (ergamisol); vaccines, e.g. anti-melanoma vaccines (see EP 0 674 097); or antibodies with

> d rn str cn

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 107868-30-4 REGISTRY

Absolute stereochemistry.



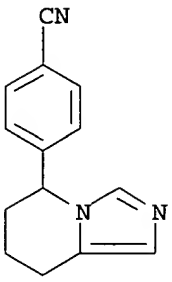
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

CN Androsta-1,4-diene-3,17-dione, 6-methylene- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 6-Methyleneandrosta-1,4-diene-3,17-dione
CN Aromasin
CN **Exemestane**
CN FCE 24304

514/177

=> d rn str cn

L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 102676-47-1 REGISTRY



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

CN Benzonitrile, 4-(5,6,7,8-tetrahydroimidazo[1,5-a]pyridin-5-yl)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Imidazo[1,5-a]pyridine, benzonitrile deriv.
OTHER NAMES:
CN **Fadrozole**

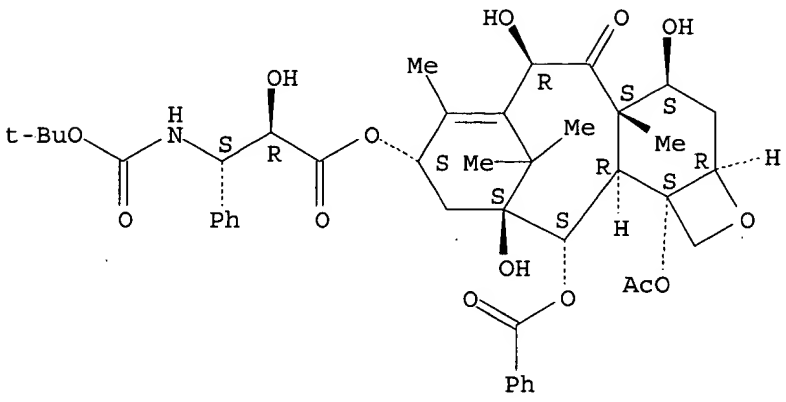
514/385, 386, 387

=> s docetaxel/cn
L4 1 DOCETAXEL/CN

=> d rn str cn

L4 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 114977-28-5 REGISTRY

Absolute stereochemistry.



CN Benzenepropanoic acid, .beta.-[[(1,1-dimethylethoxy)carbonyl]amino]-.alpha.-hydroxy-, (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, (.alpha.R,.beta.S)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 7,11-Methano-1H-cyclodeca[3,4]benz[1,2-b]oxete, benzenepropanoic acid deriv.

CN Benzenepropanoic acid, .beta.-[[(1,1-dimethylethoxy)carbonyl]amino]-.alpha.-hydroxy-, 12b-(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, [2aR-[2a.alpha.,4.beta.,4a.beta.,6.beta.,9.alpha.(.alpha.R*,.beta.S*),11.alpha.,12.alpha.,12a.alpha.,12b.alpha.]]-

OTHER NAMES:

CN **Docetaxel**

CN N-Debenzoyl-N-tert-butoxycarbonyl-10-deacetyltaxol

CN RP 56976

CN Taxotere

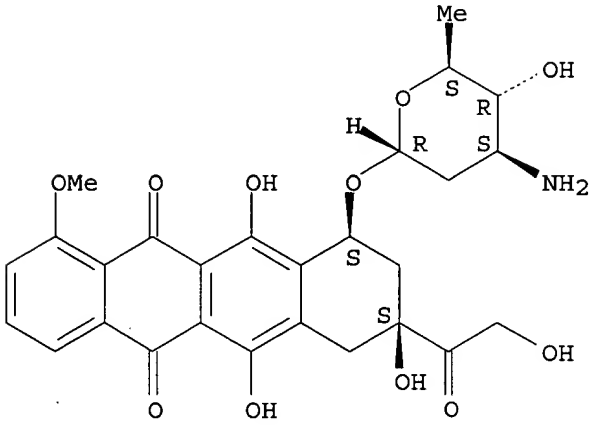
514/453

=> s epirubicin/cn
L5 1 EPIRUBICIN/CN

=> d rn str cn

L5 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 56420-45-2 REGISTRY

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-.alpha.-L-arabino-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-.alpha.-L-arabino-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S-cis)-
OTHER NAMES:
CN 4'-epi-Adriamycin
CN 4'-epi-Doxorubicin
CN 4'-Epi-DX
CN 4'-Epiadriamycin
CN 4'-Epidoxorubicin
CN Epiadriamycin
CN Epidoxorubicin
CN **Epirubicin**
CN Farmarubicin
CN Farmarubicine
CN IMI 28
CN NSC 256942
CN Pharmarubicin
CN Pidorubicin
CN WP 697

514/679
680

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=> s e3
L6            1 FLUOROURACIL/CN

=> d rn str cn

L6   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS
RN   51-21-8  REGISTRY
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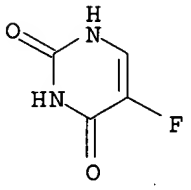

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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

CN   2,4(1H,3H)-Pyrimidinedione, 5-fluoro- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Uracil, 5-fluoro- (8CI)
OTHER NAMES:
CN   2,4-Dioxo-5-fluoropyrimidine
CN   5-Fluoracyl
CN   5-Fluoro-2,4(1H,3H)-pyrimidinedione
CN   5-Fluoro-2,4-pyrimidinedione
CN   5-Fluorouracil
CN   5-FU
CN   Adrucil
CN   Arumel
CN   Carzonal
CN   Efudex
CN   Efudix
CN   Efurix
CN   Fluoroblastin
CN   Fluoroplex
CN   Fluorouracil
CN   Fluracil
CN   Fluracilum
CN   Fluri
CN   Fluril
CN   Ftoruracil
CN   FU
CN   Kecimeton
CN   NSC 19893
CN   Phthoruracil
CN   Phtoruracil
CN   Queroplex
CN   Ro 2-9757
CN   Timazin
CN   U 8953
CN   Ulup
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514/286

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=> s mitoxantrone/cn
L7            1 MITOXANTRONE/CN

=> d rn str cn

L7   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS
RN   65271-80-9  REGISTRY
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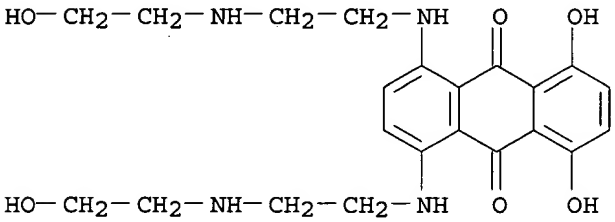

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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

CN   9,10-Anthracenedione, 1,4-dihydroxy-5,8-bis[[2-[(2-
     hydroxyethyl)amino]ethyl]amino]- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   1,4-Bis[(2-(2-hydroxyethylamino)ethyl)amino]-5,8-dihydroxyanthraquinone
CN   1,4-Dihydroxy-5,8-bis-[[2-[(2-hydroxyethyl)amino]ethyl]amino]anthraquinone
CN   1,4-Dihydroxy-5,8-bis[[2-[(2-hydroxyethyl)amino]ethyl]amino]-9,10-
     anthracenedione
CN   DHAQ
CN   Dihydroxyanthraquinone
CN   Mitoxanthrone
CN   Mitoxantrone
CN   Mitozantrone
CN   Novantron
CN   NSC 279836
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574/679
680